FIFTEEN-YEAR ARGON LASER AND XENON PHOTOCOAGULATION VISUAL RESULTS OF BASCOM PALMER EYE INSTITUTE'S PATIENTS PARTICIPATING IN THE DIABETIC RETINOPATHY STUDY*

BY *George W. Blankenship,* MD

INTRODUCTION

THE DIABETIC RETINOPATHY STUDY (DRS)[1-6] PROVIDED IMPORTANT INformation concerning the understanding and treatment of diabetic retinopathy. The natural history of the disease without photocoagulation was determined by examining a large number of patients at regular intervals for an extended time period.[4-6] Four retinopathy risk factors associated with an increased risk of severe visual loss were identified.[3] Previous reports of beneficial treatment results with xenon light and argon laser photocoagulation were confirmed.[7-14]

Numerous clinical research centers[1] participated in this large collaborative study with each center recruiting, randomizing, treating, and following patients using standardized techniques and examinations at regularly scheduled intervals. These DRS follow-up examinations were terminated in June 1979 after the study's major goals had been achieved.[6]

Many of the DRS patients being followed at the Bascom Palmer Eye Institute's clinical research center continued to return or were seen by area ophthalmologists for regular eye examinations after completion of the DRS. This paper describes the 15-year follow-up experience of those patients.

*From the Departments of Ophthalmology, University of Miami School of Medicine, Miami, Florida, and Penn State College of Medicine, Hershey, Pennsylvania. This project was supported in part by the patients and contributors of the Bascom Palmer Eye Institute, and Penn State's Department of Ophthalmology; Research to Prevent Blindness, Inc, New York City; Pennsylvania Lions Vision and Research Center; and the Breen Green Diabetic Retinopathy Fund, Miami, Florida.

METHODS

In 1988 and 1989 the original DRS records of all DRS patients recruited, randomized and enrolled, treated, and followed at the Bascom Palmer Eye Institute between 1972 and 1974 were reviewed.

Patients who were not currently being followed at the Bascom Palmer Eye Institute were traced with information obtained from the patients' original DRS records, contacted family members, and last known physicians. Surviving patients who had not been examined during 1988 or 1989 were encouraged to obtain follow-up examinations. The results of eye examinations performed during 1988 or 1989 were obtained from Bascom Palmer Eye Institute records or the patients' current ophthalmologist, and retrospectively reviewed.

Ten-year follow-up information was not available on seven of the argon laser or six of the xenon photocoagulated cases.

RESULTS

Between 1972 and 1974, 151 diabetic patients were recruited, randomized and enrolled, treated, and followed in the DRS at the Bascom Palmer Eye Institute. Within 5 years of enrollment, 35 (23%) of these patients had died. Within 10 years, a total of 71 (47%) had died, and after 15 years, 86 (57%) of the 151 patients had died. An additional 14 (9%) patients could not be located 15 years after entering the DRS, and were classified as lost to follow-up. Fifteen-year follow-up information was obtained on the remaining 51 (34%) of the original 151 patients.

In the DRS, the eye to receive treatment and the treatment modality to be used were randomly selected. Of the 51 patients examined 15 years after enrollment and treatment, 19 had been randomly assigned argon laser and 32 xenon photocoagulation.

The argon treated group consisted of 11 right and 8 left eyes assigned for treatment. There were 10 male and 9 female patients whose ages ranged from 35 to 81 years with a mean of 56 years at the time of DRS enrollment. Sixteen (84%) of the 19 patients were being maintained on insulin at the time of enrollment, and had known of their diabetes from 15 to 50 years with a mean of 33 years.

The xenon treated group consisted of 17 right and 15 left eyes assigned for treatment. There were 14 male and 18 female patients whose ages ranged from 36 to 77 years with a mean of 52 years at the time of DRS enrollment. Twenty-nine (91%) of the 32 patients were being maintained on insulin at the time of enrollment, and had known of their diabetes from 15 to 48 years with a mean of 30 years.

During the 15-year follow-up period, most of the eyes originally randomized for photocoagulation did not receive any additional photocoagulation or ocular surgery. Only one argon laser and one xenon photocoagulated eye received additional laser treatment following completion of the DRS. Four xenon treated eyes developed traction macular detachments following DRS photocoagulation and required pars plana vitrectomies. One argon treated eye required a vitrectomy for a nonclearing vitreous hemorrhage which developed approximately 7 years after initial DRS treatment. Eight argon and seven xenon treated eyes subsequently had cataract surgery, and one additional argon eye required a trabeculectomy for chronic open angle glaucoma.

Three patients whose original DRS treatment was argon laser and one xenon photocoagulated patient were requiring renal dialysis 15 years after DRS enrollment, but an additional one argon and two xenon patients had required kidney transplantation.

The best corrected visual acuities obtained just before randomization and treatment, at the last official DRS follow-up examination 3 to 5 years after treatment, and regular follow-up examinations 10 years and 15 years after treatment are shown in Table I.

DISCUSSION

The relatively high mortality rate was not surprising even though patients with severe coexistent diabetic complications or other diseases which might prevent follow-up examinations were excluded.[1] A similar 10-year mortality rate of 50% was found among patients having pars plana vitrectomies for diabetic retinopathy complications during essentially the same time period.[15] During the early 1970s hemodialysis and kidney transplantation were rarely performed for kidney failure secondary to diabetes which contributed to many of the early deaths. More recently, Klein and co-workers[16] in the Wisconsin Epidemiologic Study of diabetic retinopathy reported a 6-year survival rate for patients with proliferative diabetic retinopathy of 69.8% among 226 younger onset patients and 48.2% for 115 older onset patients.

A major effort was made to contact all potentially surviving patients, and it is probable that a large percentage of the 14 patients lost to follow-up had died. Many of these patients were older and had experienced deteriorating health with increasing diabetic and medical complications.

Visual results are only being reported on the eyes originally randomized to argon laser and xenon photocoagulation in the DRS. The fellow eyes were initially not photocoagulated and acted as controls to

TABLE I: NUMBER OF EYES AND VISUAL ACUITIES OF BASCOM PALMER EYE INSTITUTE PATIENTS PARTICIPATING IN THE DIABETIC RETINOPATHY STUDY

	PREPHOTOCOAGULATION		POSTPHOTOCOAGULATION					
			3-5 YEARS		10 YEARS		15 YEARS	
	ARGON	XENON	ARGON	XENON	ARGON	XENON	ARGON	XENON
20/15 - 20	16	23	11	10	2	2	1	2
20/30 - 40	2	7	4	10	5	11	10	11
20/50 - 70	1	2	1	5	1		1	6
20/100 - 200			2	2	3	9	6	7
15/200 - 5/200			1	3	1	3		2
L 5/200 - LP*				2		1		3
No LP							1	1
Missed exam					7	6		

*LP, light perception.

provide natural history data and to evaluate the effects of photocoagulation.[1] They became potentially eligible for argon laser photocoagulation in 1976 when there was strong statistical evidence of photocoagulation benefit when high risk characteristics were present, and the DRS protocol was appropriately changed.[2] These initial fellow or control eyes became a heterogeneous group in which some eyes had deteriorated and photocoagulation was technically impossible, some eyes received argon laser treatment consistent with original DRS protocol, some eyes had not progressed to high risk characteristics for which argon laser photocoagulation was thought appropriate, and in some cases the patients refused treatment even when recommended. The retrospective nature of this study made it impossible to determine which of several factors influenced whether or not the fellow eyes received argon laser photocoagulation.

By June 1979 when patient follow-up was terminated in the DRS, a total of 560 argon treated and 597 xenon photocoagulated eyes had been followed for 44 to 48 months since their initial randomized DRS photocoagulation treatment in all of the clinical research centers.[6] Severe visual loss defined as visual acuity of < 5/200 at two or more consecutively completed follow-up visits (visits scheduled at 4 month intervals) had occurred in 12.6% of the argon and 10.7% of the xenon treated eyes.[6] Among the Bascom Palmer Eye Institute DRS patients examined 3 to 5 years after treatment and subsequently followed for a total of 15 years, none of the 19 argon treated eyes and only 2 (6%) of the 32 xenon treated eyes had severe visual loss assuming that a similar level of decreased vision had also been present 4 months before or 4 months later.

At the end of the DRS patient follow-up in June 1979, 74 argon and 67 xenon eyes had been followed for 68 to 72 months in all the clinical research centers.[6] Severe visual loss had occurred in 17.5% of the argon and 15.9% of the xenon treated eyes. These 6-year rates are even greater than the 15-year rates of the Bascom Palmer DRS patients of which only 1 (5%) of 19 argon and 4 (12%) of the 32 xenon eyes had severe visual loss.

There may be a direct and strong relationship between this lower incidence of severe visual loss and the reduced mortality rate of the Miami patients who survived 15 years following photocoagulation. These patients may have had less severe underlying vascular disease which resulted in better preservation of vision and longer survival than other DRS recruited patients.

Little[17] reported the 10- to 12-year follow-up visual results after panretinal argon laser photocoagulation for 66 eyes with diabetic retinopathy and disc new vessels > 1/4 disc diameter in size. The eyes received an average of 3181 500-μ blue/green argon laser burns which was more than

twice the 800 to 1600 500-μ burns used in the DRS protocol. The 10- to 12-year follow-up visual results of Little's series is almost identical to the Bascom Palmer DRS cases at 10 years. Of Little's 66 cases, 37 (56%) had 20/40 or better acuity and 59 (89%) had 20/200 or better acuity, compared to 7 (58%) of the 12 argon, and 13 (50%) of the 26 xenon eyes that had 20/40 or better acuity, and 11 (92%) of the 12 argon and 22 (85%) of the 26 xenon eyes having 20/200 or better acuity at 10 years.

At 15 years the Bascom Palmer DRS visual results were similar with 11 (58%) of the 19 argon and 13 (41%) of the 32 xenon eyes having 20/40 or better acuity and 18 (95%) of 19 argon and 26 (82%) of the 32 xenon eyes having 20/200 or better acuity.[18]

Okun et al[18] has calculated that the higher incidence of harmful effects from xenon photocoagulation in the DRS was the result of more extensive photocoagulation with the DRS treatment protocol for xenon than with argon laser. This difference may account for the larger number of xenon eyes with poor acuities at each of the follow-up examinations and the larger number of xenon photocoagulated eyes requiring pars plana vitrectomy for traction macular detachments.

The previously reported beneficial treatment results with argon laser and xenon photocoagulation performed in the DRS continue to be present for those patients who survive 15 years following treatment. Some gradual visual deterioration occurs, but the incidence of severe visual loss occurring 15 years after treatment remains small.

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DISCUSSION

DR J. WALLACE MCMEEL. This excellent paper is the first long-term follow-up on a group with well documented selection and standardized treatment as afforded by the DRS. It gives insight into the general medical aspects of these patients as well as their ocular prognosis.

Three sets of data regarding the incidence of severe visual loss in the Bascom Palmer Eye Institute group are worth particular comment. First, the lower incidence of severe visual loss in eyes having argon laser rather than xenon arc photocoagulation suggests the more delicate and precise laser applications do, in fact, represent an improved technique. Second, the similar favorable results between Doctor Blankenship's and Doctor Little's long-term follow-up of panretinal photocoagulation (PRP) eyes, suggests the threshold for stabilization of retinopathy can be achieved with the lesser number of burns of the DRS protocol. Third, is the reiteration of the observation that those patients that survived the full 15 years had relatively better acuities than the larger group with documented visions 6 years after PRP. I concur with Doctor Blankenship that this probably represents a correlation between the severity of systemic and ocular vascular disease, with those having progressive retinopathy after PRP being more likely also to have life-shortening systemic complications.

One may compare the intraocular lesions of diabetes to the evolution of scar formation after tissue injury, with a sequence of physiologic insult, active re-

sponse to this insult and ultimate scar formation and quiescence. The period of active response to tissue injury is the clinical picture we classify as active angiopathy for which photocoagulation is indicated. This pathologic stage might be categorized as the zone of relative hypoxia of active angiopathy in which extensive vascular and neovascular changes, with their sequelae, occur. Prior to this stage, the eye still compensates, and if the hypoxia worsens, so that highly active metabolizing tissue dies, the active response wanes. If the levels of relative hypoxia are either above or below this zone, the active responses wanes. PRP may help to prevent the retina from remaining in this range of dangerous relative hypoxia for a prolonged period.

Our laser Doppler studies showed a rigid, significant decrease in retinal blood flow within weeks of PRP. Of interest was the local nature of this blood flow reduction, in which a photocoagulated hemisphere of fundus responded while the untreated hemisphere remained unchanged.

Our ability to create a rapid passage through a physiologically dangerous environment may partially explain the high rate of retained useful vision as compared with Beetham's pre-PRP observation that only 10% of eyes reached the late stages of retinopathy in a state of sighted benign quiescence.

New successes await us as we learn the optimal timing and techniques for PRP, how to separate the vitreoretinal interface and to uncover the causes of reactivation of quiescent angiopathy.

Dr Arnall Patz. Doctor Blankenship, in his excellent presentation, showed one graph in which the treated eyes in the DRS were protected from severe vision loss slightly greater than 50% in those treated cases. May I have the first of my two slides, please. This shows one of the patients from the early part of the diabetic studies from the Baltimore clinic. This patient has extensive disc neovascularization and hemorrhages we have noted here. This patient was recruited in the study and was typical of many of the patients who entered the DRS, particularly during early phases. In the high risk characteristics that Doctor Blankenship mentioned, a key finding is the development of disc neovascularization which we see here. This stage would be the very beginning of high risk characteristics. What I would like to point out to you is that recent studies have shown that, instead of 50% protection—when many advanced cases were included in the DRS—the protection against severe vision loss for a 5-year period is in excess of 90% if patients are treated as soon as they reach high risk characteristics. Doctor Blankenship's results suggest that this 5-year follow-up in these patients, with over 90% protection, will probably be sustained based on his 15-year follow-up.

I think that the Academy Diabetes 2000 project which he mentioned, takes on even more importance inasmuch as a large population of patients are at risk. If they are brought in for treatment at the appropriate stage—namely at the *beginning* of high risk characteristics, before the development of advanced stages, the prognosis is much better. The leadership of the AOS can be extremely helpful in getting this message out to the Academy membership. The Academy project also has a very important role in the education of the primary care physicians in

recognizing the importance of early detection and timely laser surgery, particularly since patients with proliferative retinopathy, who have not had hemorrhage, can have excellent vision and be totally asymptomatic.

I would like to congratulate Doctor Blankenship on this very timely and highly significant study he presented today.

DR HUGH R. TAYLOR. I was very interested in the visual results that Doctor Blankenship presented. I was also interested to see the relatively high mortality rate he found, with almost 60% of the original cohort having died over the 15-year period. The high mortality rate led me to ask two questions. First, how does this mortality rate compare to the mortality rate of other diabetic patients of comparable age and/or duration of diabetes? Is the presence of ocular disease a risk factor for death in diabetics, and what is the magnitude of that risk?

The second question is related, and it is, for the patients who died, were there any characteristics, either at baseline, in their response to treatment, or at their last examination, that would identify risk factors or associated ocular changes that may indicate an increased risk of dying?

DR D. JACKSON COLEMAN. I would like to commend Doctor Blankenship on this excellent presentation. I just have two questions. The first is a question regarding field changes. The acuities are usually measured but the effectiveness of maintaining sight in terms of field is also important. Was there any attempt to judge what field or night vision results might be different between the two groups? Second, can you suggest a better way of evaluating visual function?

DR PAUL C. WETZIG. I am very happy to learn from Doctor Blankenship the follow-up of the final visual results of these early treatments. I would like to make a few historical comments. At the onset of the concept of this method of treatment, the only apparatus available for treatment was the xenon photocoagulator manufactured by Zeiss. This instrument was used on all of the patients for a number of years. Finally, with the advent of the argon laser the slit lamp delivery system became more sophisticated and easier to use, and with the marketing tactics of the companies the xenon photocoagulator was gradually pushed into oblivion. As a result, most of the young people training in photocoagulation had no experience at all with the xenon apparatus and this instrument was relegated to the museums.

I think that the basic difference in the modality of treatment, if there is any in these two methods of treatment, is not related to the light source, per se, because all of the light sources will produce a retinal burn. The basic difference is in the delivery system. The delivery system of the slit lamp is certainly more precise and the applications more discrete. However, there are still some advantages to the xenon apparatus. When the media is hazy, or when there is a projection of material into the vitreous, the xenon apparatus still has a useful application. I recently saw a patient who had a very successful result with a xenon photocoagulation, but required more treatment. This is always upsetting to the patient. On

going to another physician, the patient was advised that he had been treated with something that was obsolete 20 years ago. I am very grateful to Doctor Blankenship for documenting the similarity of the final visual results in the argon versus xenon treated patients.

DR HUNTER L. LITTLE. I would also like to commend Doctor Blankenship on a fine paper. I am happy and not surprised that the results are in agreement with our study of 5- to 10-year follow-up published in 1983 in ACTA:XXIV International Congress of Ophthalmology.

Interesting findings in our study of 241 eyes, treated with argon PRP for diabetic disc new vessels, were the similarities of results after 5 and 10 years follow-up. In both groups, 60% had 20/50 or better visual acuity, and the total number of 500 μ lesions averaged 3200 after 5-year, and 3600 after 10-year follow-up. Once retinopathy was quiescent for 3 to 5 years, retinopathy and vision usually remained stable. I was surprised that none of your cases required additional treatment during the first 1 to 2 years after the initial course of PRP, as many of our cases did.

Another observation in our study was the absence of macular edema in eyes 5 and 10 years following PRP with the proviso that macular edema was not present prior to PRP. Even though PRP may exacerbate preexisting macular edema, PRP may reduce the risk for eyes developing macular edema in the future; ie, PRP may well provide a protective effect on preventing diffuse macular edema. In the absence of macular edema at the time of treatment, did any of your cases develop diffuse macular edema?

DR GEORGE W. BLANKENSHIP. I would like to thank the discussants, especially Doctor McMeel, for their pertinent comments, and to respond to their questions.

Several comments were made comparing argon and xenon, and I agree with Doctor Wetzig that the poorer DRS results with xenon had nothing to do with the xenon wavelengths. The treating physicians in the DRS were a relatively young group without the years of experience that Doctor Wetzig and many of you had in using xenon photocoagulation. The results of experienced physicians using xenon do not have the complications that occurred in the early phase of the DRS. Doctor Okun has frequently spoken about the DRS and the tendency to be too critical of xenon photocoagulation.

The amount of photocoagulation required to regress neovascularization varies from eye to eye. An amount of treatment is used initially that we believe will be successful in regressing neovascularization in most eyes. Adequate treatment may be the 1200 burns used in the DRS or more burns may be needed. In general, we use more treatment today than in the DRS, but once neovascular regression has been obtained, that is usually all that is needed.

There is confusion about life tables, which is how much of the DRS data has been presented. The 15-year follow-up data is presented as a percentage distribution of visual acuities. Comparing these two different types of tables is like comparing apples and oranges. For this 15-year data to be comparable to the DRS

life tables, the last visual acuities of all the patients that had died during the 15 years would have to be determined and added to the percentage distribution.

Doctor McMeel, I agree with you that photocoagulation, while we do not know how it works, rapidly passes the eye through this vulnerable period of peak vascular proliferation avoiding many of the complications that occur with diabetic retinopathy.

Doctor Patz commented about the stability of the survivors. This is a group of people who are surviving their disease longer either because of genetics, better medical control, or other presently unknown factors. Perhaps these same factors predispose the survivors to preserve good vision, but it was impossible to retrospectively obtain the acuities of the patients that died with which to compare. When the DRS was actively following patients, a tremendous emphasis was placed on getting all surviving patients back for scheduled examinations at regular intervals regardless of their visual and physical status. Once the study was over, some patients who were doing well were less motivated to return. Others with more serious disease deterioration found it physically difficult to return. Often loss of vision was a relatively minor problem, compared to some of the other complications of their diabetes.

Doctor Taylor spoke to us about the mortality rate. Other diabetic retinopathy studies have mortality rates similar to this population. A few years ago Doctor Machemer and I found that exactly 50% of patients had died 10 years after having had pars plana vitrectomies for diabetic retinopathy. Other than the obvious, there wasn't anything particular about the fundus pictures or the patients that indicated those who were going to die and those who were going to survive.

Doctor Coleman, 15-year follow-up visual fields were not measured and I do not know if there is further loss of field or dark adaptation with time, or if there are differences between argon and xenon changes.

Again, Doctor Wetzig, I think you are right—that there is a role for xenon photocoagulation. The loss of xenon photocoagulation is related more to the excellent marketing and the public appeal of the word laser, and the ease of treating patients and teaching residents how to use laser as compared with xenon rather than with the results.

For years I have followed Doctor Little's work and learned from his very large series of cases. The 10- to 12-year follow-up report of eyes with disc neovascularization had over 100 patients. Like this large series, not one case in this 15-year DRS group developing cystic or extensive exudative macular edema. Many of them had a loss of vision from macular ischemia but none developed extensive macular edema.